Remarks

Claims 9 and 13-18 are pending and under consideration. With this Amendment, Claims 9 and 13-18 are being cancelled, without prejudice against their reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications, and claims 19-24 are being newly added. Thus, after entry of this Amendment, claims 19-24 are pending and under consideration. The amendments of the claims and the various rejections raised in the Office Action are discussed in more detail below.

I. The Amendments to the Claims

Claims 9 and 13-18 have been cancelled and replaced with claims 19-24. Support in the specification for the new claims are as follows.

Claim 19 finds support in the specification on page 5, lines 26-32; and page 16, lines 10-16.

Claims 20 to 23 find support throughout the specification, such as on page 3, line 28 extending through to page 4, line 14; and page 8, line 27 extending through to page 9, lines 21.

Claim 24 finds support in the specification on page 5, lines 14-16.

In view of the foregoing, no new matter is added by way of the amendments. Entry of the amendments is therefore respectfully requested.

II. Rejections Under 35 U.S.C. § 102

Claims 9 and 13-18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by US Patent No. 5,542,935 to Unger et al. ("Unger"). Applicant traverses the rejection as applied to claims 19-24.

A. The Present Claims

The present claims relate to administering parenterally to a subject a composition comprising perfluorobutane microbubbles containing an antiproliferative chemotherapeutic agent, wherein the microbubbles are encapsulated with human serum albumin, and allowing the agent to be released at the tumor site without the use of external stimulation.

B. The Cited Art

Unger describes liposome or micellar microparticles useful as ultrasound contrast agents and/or as therapeutic delivery vehicles. The lipid based microparticles are prepared in presence of an inert gas (i.e., gas precursor), such as perfluorobutane:

> Methods of preparing the temperature activated gaseous precursor-filled *liposomes* include: vortexing an aqueous suspension of gaseous precursor filled *liposomes* of the present invention, variations of this method include optionally heating an aqueous suspension of gaseous precursor and lipid . . . . Freeze drying is useful to remove water and organic materials from the *lipids* prior to the shaking gas instillation method. As the *dried liposomes* are kept at a temperature below their gel state to *liquid crystalline temperature* the drying chamber can be slowly filled with the gaseous precursor in its gaseous state, e.g., perfluorobutane can be used to fill dried *liposomes* composed of *dipalmitoylphosphatidylcholine* (DPPC) at temperatures between 3°C (the boiling point of perflurobutane, and below 40°C, the *phase transition temperature of the lipid*. In this case, it would be most preferred to fill the *liposomes* at a temperature about 4°C to about 5°C.

See Unger, column 13, line 34 through to column 14, line 10 (emphasis added). Further, the properties of the microparticles are described as follows:

> *Liposomes* are a preferred embodiment of this invention since they are highly useful for entrapping gas. . . . The yield of gas filled *lipid* spheres produced from gaseous precursors increases when prepared from *hydrated multilamellar lipid suspensions* as opposed to large unilamellar vesicles or dried lipid. . . . The *lipid in the gaseous precursor-filled liposomes may be in the form of a single*

> *bilayer or a multilamellar bilayer*, and are preferably multilamellar. Lipids with may be used to create liposome microspheres include, but are not limited to lipids such as fatty acids, lysolipids . . . .

See Unger, column 20, lines 4-67 (emphasis added). Based on the descriptions in the specification, Unger emphasizes liposome based microparticles and microbubbles filled with a gas or gas precursor.

C. Claims Are Not Anticipated By Unger

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *see also* M.P.E.P. § 2131. The identical invention must be shown in as complete detail as it is contained in the claim." *See Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Moreover, the knowledge must be sufficiently enabling to place the information in the possession of the public. *See In re Omeprazole Patent Litigation*, 82 USPQ2d 1643 (Fed. Cir. 2007).

In the rejection, the Patent Office characterizes the reference of Unger ("the '935 patent") as disclosing microbubbles encapsulated with human serum albumin, where the microbubbles are filled with perfluorobutane. However, the Unger disclosure emphasizes liposomes and micelles filled with perfluorocarbon gas. References to "liposomes", "micellar" and "crystalline temperature" are unmistakably descriptions of lipid-based microparticles. The Patent Office points to column 22, lines 50-63 of Unger as describing microbubbles with a coating of human serum albumin. However, the cited passage refers to emulsifying and stabilizing agents to control the size of the precursor filled microsphere and to stabilize the microsphere. These agents are considered optional:

> Although stabilization of the microsphere is preferred, this is not an absolute requirement. . . . One or more stabilizing agents is preferred however as are flexible stabilizing materials. Gas

> microsphere stabilized by albumin and other proteins are less effective as these stabilizing coating are more brittle and are easily broken during pressure changes, for example by passage through the heart and arteries. *Liposomes* prepared using aliphatic compounds are preferred as microsphere stabilized with these compounds are much more flexible and stable to pressure changes. . . . Solutions of *lipids* or gaseous precursor filled *liposomes* may be stabilized, for example, by the addition of a wide variety of viscosity modifiers . . . .

See Unger, column 22, line 60 to column 23, line 12 (emphasis added). Thus, Unger describes use of serum albumin as a stabilizing agent in the context of liposomes. Although Unger generally describes a list of other components for forming microparticles, Unger does not specify which of the various types of microparticles formulations are useful as a ultrasound contrast agent, a vehicle for delivery of therapeutic compounds, or both.

In contrast to Unger, the instant claims specifically recite microbubbles in which the perfluorobutane gas is entrapped using a filmogenic protein, namely human serum albumin. Synthesis of the microbubbles are described:

> In a typical procedure, 5% human serum albumin and 5% dextrose, obtained from commercial sources, were drawn into a 35 mL syringe in a 1:3 ratio, hand agitated with 6-10 mL of decafluorobutane, and sonicated at 20 kilohertz for 75-85 second.

See Specification, page 16, lines 10-12. Clearly, the microbubbles of the instant claims do not require liposomes or micelles. Moreover, the claims specify that the microbubbles contain an antiproliferative chemotherapeutic agent. Unger's emphasis on use of gas-filled liposomes, and description of only general features of other microparticle formulations without specifying which formulation is to be used for effective delivery of a specific class of chemotherapeutic compounds, is not a sufficient basis to support an anticipation rejection. Unger does not set forth each and every element of the instant claims, and therefore does not anticipate the claims under 35 U.S.C. § 102. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejections Under 35 U.S.C. § 103(a)

Claims 9 and 13-18 are rejected under 35 U.S.C. § 103(a) as being obvious over US Patent No. 5,542,935 to Unger et al. ("Unger"). Applicant respectfully traverses the rejection as applied to claims 19-24.

A. Legal Standard for Determining Obviousness

Determining obviousness under 35 U.S.C. § 103(a) requires an objective analysis involving four factual inquiries, which include:

(a) determining the scope and content of the prior art,
(b) ascertaining the differences between the prior art and the claims in issue;
(c) resolving the level of ordinary skill in the art; and
(d) evaluating evidence of secondary considerations.

See Graham v. John Deere, 383 US 17, 18, 148 USPQ 459, 467 (1966); *see also* M.P.E.P. § 2141. A claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1385 (US 2007). It is also important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *See id.* Thus, in assessing the scope and content of the prior art, the references must be considered in its entirety, *i.e.*, as a whole including portions that would lead away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 US 851 (1984); *see also* M.P.E.P. § 2141.02.

Moreover, there must be a reasonable expectation of success. *See* M.P.E.P. § 2141. Hence, the obviousness analysis should consider whether the claimed invention is a predictable variation of the prior art elements. *See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1385 (US 2007); *see also* M.P.E.P § 2141.

B. Claims Are Not Obvious Over Unger

As summarized above, Unger discloses perfluorocarbon gas-filled liposomes and micelles for use as contrast agents and/or for delivery of therapeutic compounds. In Unger, a lipid layer is used to entrap the gas (or gas precursor). Unger also describes generally other components for forming microspheres, but Unger does not specify which of these various microsphere formulations are to be used as a ultrasound contrast agent, a vehicle for delivery of a chemotherapeutic agents, or a formulation suitable for both types of uses. In constrast, the instant claims recite use of microbubbles formed by encapsulating a perfluorocarbon gas with a filmogenic protein, namely human serum albumin. The composition of the microbubbles of the instant application are not the same or similar to liposomal microspheres in Ungar since lipids used to form liposomes have different properties than filmogenic proteins, and thus do not represent a simple replacement of a component (i.e., lipid) with similar chemical properties. Moreover, any description for use of proteins in the gas precursor filled microsphere is contradicted by Unger's own statement on the effect of proteins in the microspheres:

> Although stabilization of the microsphere is preferred, this is not an absolute requirement. . . . One or more stabilizing agents is preferred however as are flexible stabilizing materials. Gas microsphere stabilized by albumin and other proteins are less effective as these stabilizing coating are more brittle and are easily broken during pressure changes, for example by passage through the heart and arteries. Liposomes prepared using aliphatic compounds are preferred as microsphere stabilized with these compounds are much more flexible and stable to pressure changes.

See Unger, column 22, line 60 to column 23, line 12 (emphasis added). Clearly, Unger not only makes use of proteins as stabilizing optional, but directs the skilled artisan away from considering the use of proteins in the microparticle liposomes. Thus, Applicant submits that Unger teaches away from use of proteins in the microspheres of the instant claims.

When the Unger is viewed as a whole, the reference does not provide sufficient teaching or suggestion of all of the claim limitations, nor does it prompt a skilled artisan

to choose a particular formulation of a filmogenic protein for therapeutic delivery of a specific class of chemotherapeutic compounds. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

IV. Conclusion

Claims 19-24 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested. Should any unresolved issue remain in the application and is better addressed by a conference, the Examiner is encouraged to contact the undersigned representative at telephone number 650.838,4365.

No fees beyond those submitted herewith are believed to be due in connection with this Amendment. However, the Director is authorized to charge any additional fees that may be required, or credit any overpayment, to Perkins Coie LLP Deposit Account No. 50-2207 (**Order No. 50450-8060.US00**).

Respectfully submitted,

Date: October 31, 2007 / Euk Oh /

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